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(54) Title: PHARMACEUTICAL FORMULATIONS

(57) Abstract: The present invention relates to salts of a biodegradable polymeric sugars comprising acidic groups and a pharmaceutically active agent comprising one or more basic groups, and to pharmaceutical formulations of said salts adapted for administration by inhalation.

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PHARMACEUTICAL FORMULATIONS

The present invention is concerned with pharmaceutical formulations of active agents, in particular salts of polymeric sugars with pharmaceutically active agents useful for administration by inhalation, e.g. in the prophylaxis and treatment of respiratory diseases, salts of polymeric sugars with pharmaceutically active agents, processes for their preparation and their use in medicine.

Pharmaceutically active agents for the prophylaxis and treatment of respiratory diseases, e.g. asthma, are commonly administered by inhalation of particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, dry powder inhalers, nebulisers or insufflators. Inhalation of drugs to the lungs or the nasal mucosa is also a useful route for administration of other pharmaceutically active agents, in particular because this route can result in rapid onset of action of the active agent.

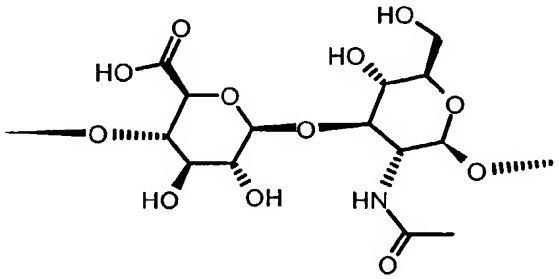
Dry powder inhalers typically use a carrier such as lactose as a diluent to allow precise metering of the dose and to facilitate dispersion of the active agent on inhalation by the patient. Some lactose formulations can be prone to degradation on storage which can result in reduction of the the dose delivered to the lungs thus requiring careful control of the shelf life. For adequate penetration of the active agents into the lungs particles having an aerodynamic particle size of less than 20μm, e.g. from 1-10μm, particularly 2-5μm, are required. Thus it is important that dry powder formulations exhibit stability with relation to the quantity of particles of this size that they contain.

Generally salts of respiratory drugs are provided in the form of a crystalline salt, as crystalline salts are generally believed to have favourable physical properties such as defined hygroscopicity and aqueous solubility and/or good stability. For example the β_2-adrenoreceptor agonist salmeterol is currently formulated for administration as a crystalline xinafoate salt.

The present invention is based on the finding that an amorphous salt of salmeterol with hyaluronic acid exhibits surprisingly advantageous properties, particularly when formulated as a formulation, e.g. a dry powder formulation, adapted for administration by inhalation.

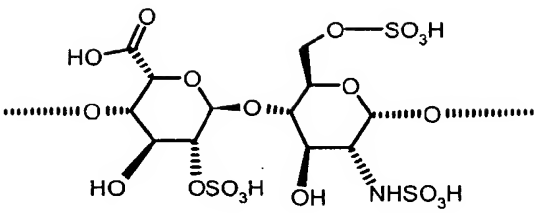
A number of biodegradable polymeric sugars bearing acid or base functionality are known, these include hyaluronic acid, heparin/heparan sulfate, dermatan sulfate, chondroitin sulfate, keratin sulfate, alginic acid and salts thereof.

Hyaluronic acid (CAS registry number 9004-61-9), also known as hyaluronan, is a naturally occurring polymeric sugar with a molecular weight of about $2x10^5$ to $2x10^6$ Da which is formed of repeating disaccharide units of glucuronic acid and *N*-acetylglucosamine. The chemical representations of hyaluronic acid and the other polymeric sugars given below are for purposes of illustration only, and show the repeating disaccharide units present in the polymeric chain.



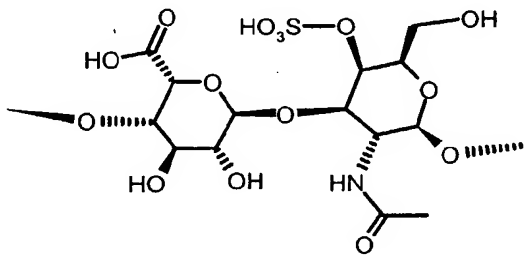
Hyaluronic acid is widely found in connective tissues of humans and animals, e.g. skin, vitreous and aqueous humor, umbilical cord and synovial fluid. Hyaluronic acid has been used as a medicinal excipient, for example in biomaterials and viscoelastic solutions for intra-articular and ophthalmic delivery. Hyaluronic acid is available from a number of commercial sources.

Heparin (CAS registry number 9005-49-6) and heparan sulfate (CAS registry number 9050-30-0) both have the same basic structure of repeating disaccharides units of glucuronic acid and *N*-acetylglucosamine. Both polymers contain numerous variations of sulfonation and L-epimerisation. They are commonly differentiated by the proportion of *N*-sulfonation, heparan sulfate generally being considered to have less than 50% and heparin generally greater than 70%. Individual chains can reach $1x10^5$ Da but are normally below $5x10^4$ Da.

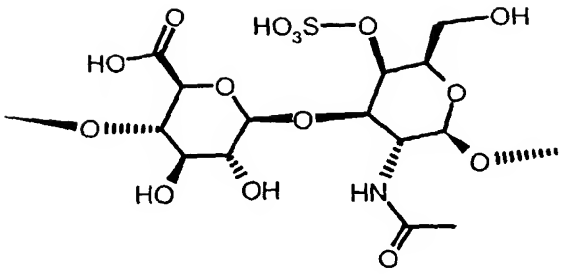


Heparin is widely known for its anti-coagulant action, based on its binding with antithrombin III. Heparin is available from a number of commercial sources.

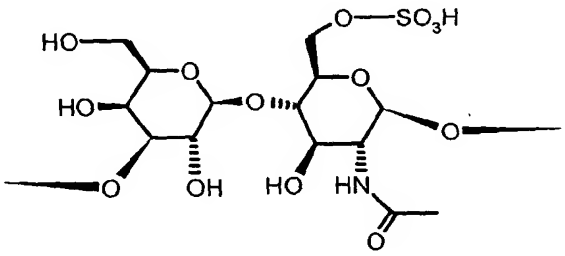
Dermatan sulfate (CAS registry number 24967-94-0) is another example of a naturally occurring polymeric sugar, having a molecular weight of about $1x10^4$ to $4x10^4$ Da, it is formed of repeating disaccharide units of hexuronic acid (either glucuronic acid or its epimerised form iduronic acid, both forms can be found in one individual carbohydrate chain) and *N*-acetylgalactosamine. The disaccharide is often sulfonated in position 2 of the iduronic acid or position 4 of *N*-acetylgalactosamine. Dermatan sulfate is available from a number of commercial sources.



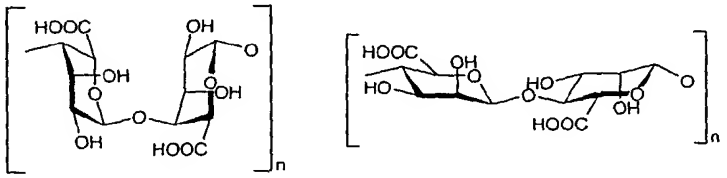
Chondroitin sulfate (CAS registry number 9007-28-7) consists of disaccharides containing glucuronic acid and *N*-acetylgalactosamine, it is the most common glycosaminoglycan form found in articular cartilage. The molecular weight of a single chain is typically in the region of $1x10^4$ to $2x10^4$ Da. The component disaccharides are often sulfonated at position 4 or 6 of the *N*-acetylgalactosamine, although unsulfonated, di- and tri-sulfonated forms have been observed. Chondroitin sulfate is available from a number of commercial sources.



Keratan sulfate (CAS registry number 9056-36-4) consists of repeating units of galactose and *N*-acetylglucosamine, demonstrating variation in molecular weight from around $4x10^3$ to $2x10^4$ Da; variation in the degree of sulfonation is also observed. Certain forms of keratin sulfate may contain fucose and *N*-acetyl neuraminic acid groups in their chains, while chain branching is also known to occur. Keratan sulfate is available from a number of commercial sources.



Alginic acid (CAS registry number 9005-32-7) is a polysaccharide which is obtained from seaweed. Alginic acid contains mannuronic acid and guluronic acid residues, the proportions of each being dependent upon the species of seaweed from which it is extracted. The two sugar monomers often occur in blocks of up to twenty units, the number and length of the blocks being an important factor in determining the physical properties of the chains.



A number of salt forms of alginic acid are known (not all of which are soluble in water) for example sodium alginate (CAS registry number 9005-38-3).

International Patent Application WO 95/26735 discloses the use of hyaluronic acid for the treatment of respiratory disorders. International Patent Application WO 01/93846 discloses the use of polysaccharides, including hyaluronic acid, for the prophylaxis and treatment of elastic fiber injury in mammals. International Patent Application WO 02/102317 discloses the use of hyaluronic acid for the treatment of tissue kallikrein-induced bronchoconstriction. US Patent Application 2003/0171332 describes the use of aerosolised polysaccharides, including hyaluronic acid, for the treatment of respiratory conditions associated with tissue kallikrein-induced bronchoconstriction. This application only exemplifies solutions of hyaluronic acid for administration by nebulisation, it does not exemplify solid particulate formulations for inhalation.

Japanese Patent Application 11171761 discloses inhalation formulations comprising drug microparticles, e.g. beclomethasone propionate, coated with a biodegradeable and bioadhesive polymer e.g. sodium hyaluronate. Journal of Controlled Release, Sept 4, 2003, 91(3), 385-94 describes the preparation of a dry powder for inhalation comprising co-spray drying sodium hyaluronate and human insulin.

Japanese Patent Application 11080032 discloses pharmaceutical compositions comprising a basic drug and an acidic polysaccharide.

International Patent Application WO 00/08061 discloses cosmetic and pharmaceutical compositions comprising amino acid salts of hyaluronic acid e.g. lysine hyaluronate. International Patent Application WO 98/17285 discloses compositions for topical administration comprising a neutral salt of hyaluronic acid and a basic anaesthetic, e.g. benzydamine or bupivacaine, it does not disclose solid particulate formulations of these salts for inhalation. Ophthalmic Research, 1998, 30(2), 101-106 discloses timolol and pilocarpine hyaluronate salts for the treatment of ocular hypertension.

According to the present invention there is provided a pharmaceutical formulation adapted for administration by inhalation, comprising a salt of a biodegradable polymeric sugar comprising acidic groups and a pharmaceutically active agent comprising one or more basic groups, and a pharmaceutically acceptable carrier or diluent.

The salt of a biodegradable polymeric sugar comprising acidic groups and a pharmaceutically active agent comprising one or more basic groups is hereinafter referred to as a "salt of the invention".

Biodegradable polymeric sugars comprising acidic groups which may be used to form the salts of the invention include hyaluronic acid, chondroitin sulfate e.g. chondroitin sulfate A, B or C, alginic acid, keratin sulfate and heparan sulfate. As mentioned above these sugars comprise carboxylic acid and/or sulfonic acid groups. The acidic groups are preferably carboxylic acid groups.

Pharmaceutically active agents which are suitable for formulation as salts according to the invention include agents comprising basic group(s) having a pKa $\geq$6, preferably a pKa of 7-12 in the case of sugars comprising carboxylic acid groups (e.g. hyaluronic acid and alginic acid); and a pKa $\geq$4, preferably a pKa of 4-12 in the case of sugars comprising sulfonic acid groups (e.g. keratan sulfate); and a pKa $\geq$4, preferably a pKa of 4-12 in the case of sugars comprising both sulfonic acid groups and carboxylic acid groups (e.g. chondroitin sulfate, heparin, heparan sulfate). In the case of other acid groups that the sugar may comprise, the preferred pKa of the basic group(s) of the pharmaceutically active agent may be determined by reference to the strength of the acid.

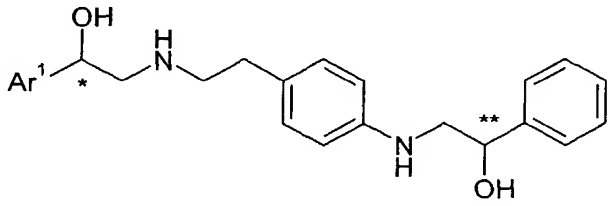
Pharmaceutically active agents containing one or more amine groups, e.g. primary, secondary or tertiary amine groups, are preferred.

The invention also provides a salt of a biodegradable polymeric sugar comprising acidic groups and a pharmaceutically active agent containing one or more amine groups.

Specific pharmaceutically active agents which may be mentioned include β_2-adrenoreceptor agonists, anti-inflammatory agents (e.g. NSAIDs or PDE-4 inhibitors), anticholinergic agents (e.g. M_1, M_2, M_1/M_2 or M_3 receptor antagonists), antiinfective agents (e.g. antibiotics, antivirals) and antihistamines.

Examples of β_2-adrenoreceptor agonists include salmeterol, (R)-salmeterol, salbutamol, (R)-salbutamol, formoterol, (R,R)-formoterol, fenoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerobuterol, reproterol, bambuterol and terbutaline.

Other examples include those described in International Patent Applications WO 02/066422, WO 02/070490, WO 02/076933, WO 03/024439, WO 03/072539, WO 03/091204, WO 04/016578, WO2004/022547, WO 2004/037807, WO 2004/037773, WO 2004/037768, WO 2004/039762 and WO 2004/039766, for example
3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl)benzenesulfonamide;
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide;
4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol; and
4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol.
Other β_2-adrenoreceptor agonists include QAB-149, LAS-32521, [R-(R*,R*)]-8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolone (CAS-137888-11-0);
N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;
5-[(R)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one;
and the following compounds described in International Patent Application WO 01/42193:



wherein Ar^1 is 4-amino-3,5-dichlorophenyl or 3-formylamino-4-hydroxyphenyl, and the stereochemistry at *C and **C is (RS) and (RS), (R) and (R), (S) and (S), (R) and (S), or (S) and (R), e.g *N*-{2-[4-((*R*)-2-Hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine;

Examples of NSAIDs include phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin

antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis.

Examples of antihistamines (also referred to as H1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H1-receptors, and are safe for human use. First generation antagonists, include derivatives of ethanolamines, ethylenediamines, and alkylamines, e.g. diphenylhydramine, pyrilamine, clemastine, chlropheniramine. Second generation antagonists, which are non-sedating, include loratidine, desloratidine, terfenadine, astemizole, acrivastine, azelastine, levocetirizine fexofenadine and cetirizine.

Examples of antimuscarinic antagonists include 2-[(*S*)-1-(8-methylaminooctyl)-pyrrolidin-3-yl]-2,2-diphenylacetamide.

In one embodiment salts of the invention include salts of amine containing pharmaceutically active agents, e.g. primary, secondary or tertiary amine containing pharmaceutically active agents. In a particular embodiment pharmaceutically active agents are amine containing β_2-adrenoreceptor agonists.

A particular salt of the invention is salmeterol hyaluronate.
Other salts of the invention which are of interest are salbutamol hyaluronate, 4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol hyaluronate;
N-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine hyaluronate; and
2-[(*S*)-1-(8-methylaminooctyl)-pyrrolidin-3-yl]-2,2-diphenylacetamide hyaluronate.

Pharmaceutical formulations containing salts of the invention may also comprise one or more other pharmaceutically active agents, e.g. selected from the lists defined above.

Formulations containing salts of β_2-adrenoreceptor agonists may desirably also contain a glucocorticoid receptor agonist. Examples of glucucorticoid agonists include steroids such as budesonide, ciclesonide, triamcinoline acetonide and beclomethasone dipropionate. Further examples of glucucorticoid agonists include steroids such as fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-

thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

The biodegradable polymeric sugar when employed according to the invention may typically have a molecular weight of around 10^4-10^6 Da.

A particular biodegradable polymeric sugar for use in the invention is hyaluronic acid.

The maximum possible loading of the pharmaceutical active agent onto the biodegradable polymeric sugar can be determined theoretically by reference to the specific agent and sugar. For example when the polymeric sugar is hyauronic acid, the maximum loading is around 2.5mmol/g (i.e. 2.5 mmol of active agent per g of sugar). When the polymeric sugar is alginic acid, the maximum loading is around 5mmol/g. When the polymeric sugar is chondroitin sulfate or dermatan sulfate, the maximum loading is around 4mmol/g. When the polymeric sugar is keratan sulfate the maximum loading is around 2 mmol/g. When the polymeric sugar is heparin or heparan sulfate, the maximum loading is around 6 mmol/g. Preferably a loading of less than maximum is employed e.g. 50-75% of maximum. Lower loadings of drug, e.g. of about 25% of maximum may be particularly advantageous for highly potent drugs. When the biodegradable polymeric sugar is hyaluronic acid and the drug substance has molecular weight of approximately 500 Da the maximum loading capacity of pharmaceutically active agent in the salts of the invention is around 55% w/w (i.e. weight of pharmaceutically active agent / weight of salt). For the loading of a drug substance of molecular weight of approximately 500 Da loadings are typically between 5–40% w/w. Lower loadings of drug, e.g. of about 10% w/w may be particularly advantageous for highly potent drugs.

The pharmaceutical formulations and salts of the invention have use in the prophylaxis and treatment of diseases treatable by administration of an active agent by inhalation e.g. respiratory diseases. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis).

Accordingly, the present invention provides a method for the prophylaxis or treatment of disease in a mammal which comprises administration by inhalation of a therapeutically effective amount of a pharmaceutical formulation or a salt according to the invention.

The invention also provides a method for the prophylaxis or treatment of a respiratory disease, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation or a salt of the invention. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

In the alternative, there is also provided a pharmaceutical formulation or a salt of the invention for use in medical therapy, particularly, for use in the prophylaxis or treatment of a respiratory disease in a mammal, such as a human. In particular, there is provided a pharmaceutical formulation or a salt of the invention for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

The present invention also provides the use of a pharmaceutical formulation or a salt of the invention in the manufacture of a medicament adapted for administration by inhalation.

The invention also provides the use of a pharmaceutical formulation or a salt of the invention in the manufacture of a medicament for the prophylaxis or treatment of a respiratory disease, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

More generally, the pharmaceutical formulations and salts of the invention may be formed with pharmaceutically active agents, such as morphine and codiene, which treat non-respiratory conditions for which administration by inhalation is beneficial e.g. to achieve rapid delivery to the system.

The amount of the salt of the invention which is required to achieve a therapeutic effect will, of course, vary with the particular active agent the subject under treatment, and the particular disorder or disease being treated. The salts of the invention may typically be

administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.02mg to 2mg. The dose range for adult humans is generally from 0.0005 mg to 5mg per day and preferably 0.01 mg to 1mg per day depending on the loading of active agent in the salt.

Preferably the amount of polymeric sugar which is administered to a human is such that it does not have any pharmacological effect, especially when the polymeric sugar is hyaluronic acid.

While it is possible for a salt of the invention to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Pharmaceutical formulations suitable for inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators, the most suitable route of generation may depend upon, for example, the condition and disorder of the patient.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the salt of the invention into association with the carrier which may contain one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the salt of the invention with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

The pharmaceutical formulations and salts of the invention are preferably formulated as dry powder compositions for topical delivery to the lung by inhalation. Dry powder compositions may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the salt of the invention and a suitable powder base (carrier substance) such as lactose or glucose. Use of lactose is preferred. Alternatively, the salt of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (e.g. as in Diskus™, see GB 2242134 or Diskhaler™, see GB 2178965, 2129691 and 2169265) or metered in use (e.g. as in Turbuhaler™, see EP 69715 or EP237507). An example of a unit-dose device is Rotahaler™ (see GB 2064336). The Diskus™ inhalation device

comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a salt of the invention preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet. Alternatively, the formulation may be presented if desired together with one or more other therapeutic agents in an inhalation device wherein the individual therapeutic agents are administrable simultaneously but are stored separately (or wholly or partly stored separately for triple combinations), e.g. in separate pharmaceutical compositions, for example as described in WO 03/061743.

Each capsule, cartridge, pouch or blister may typically contain between 1μg-3mg e.g. 10-500μg of the salt of the invention optionally in combination with another therapeutically active ingredient and optionally together with one or more carriers.

Spray compositions for topical delivery to the lung by inhalation may also be formulated as suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the salt of the invention optionally in combination with another therapeutically active agent and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants e.g. oleic acid or lecithin and cosolvents e.g. ethanol. Pressurised formulations will generally be retained in a canister (e.g. an aluminium canister) closed with a valve (e.g. a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum aerodynamic particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the salts of the invention may be size reduced by conventional means e.g. by micronisation or spray dried from a solution to yield particles of the desired size (i.e. mass median diameter (MMD) of 1-10μm, preferably 2-5μm).

A salt of the invention is suitably provided in particulate form, particularly in the form of a micronised or spray-dried product.

When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the salt of the invention. When the excipient is lactose it will typically be present as milled lactose, wherein at least 85% of lactose particles have a MMD of 60-90μm and not more than 15% have a MMD of less than 15μm.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active agent.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of the invention may include other agents conventional in the art having regard to the type of formulation in question. For example alkaline earth stearates, e.g. magnesium stearate, may be added to increase the dose delivered to the lungs and to prevent decline of this on storage. Other agents, which may e.g. be blended in an amount of 1-10% w/w with lactose, include cellobiose octaacetate as described in WO03/088943.

The pharmaceutical formulations and salts of the invention may also be administered in combination with one or more other pharmaceutically active agents, e.g. for the treatment of respiratory diseases. Such combinations may conveniently be presented in the form of a pharmaceutical formulation and thus pharmaceutical formulations adapted for

administration by comprising a combination as defined above together with a physiologically acceptable diluent or carrier is a further aspect of the invention.

The pharmaceutical formulations and salts of the invention and the other pharmaceutically active agents may be administered separately, sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known active agents will be readily appreciated by those skilled in the art.

The salts of the invention and pharmaceutical formulations thereof have the potential to offer certain advantages over known forms of pharmaceutically active agents for administration by inhalation. Without wishing to be bound by theory it is believed that salts of the invention formed by binding of an active agent to a given polymeric sugar may be expected to result in salts having equivalent physical properties. This should enable all said salts to be formulated in the same way, thus simplifying pharmaceutical development. For inhaled products this has potential benefits for potent ionisable active agents which require low blend strengths as the potency of the drug can be diluted by changing the drug loading on the polymer. The drug/polymer compound can then be micronised and blended with e.g. lactose in the normal way. The need for classical salt selection could also be eliminated thus enabling drugs to be developed more quickly. There is also the potential for both slow release and once daily products and improved drug stability in the presence of carriers such as lactose.

The salts of the invention are amorphous and as such there is no opportunity for conversion to other polymorphic forms as may be the case with crystalline forms of active agent; this can be particularly advantageous for dry powder formulations. The amorphous nature of the salts also offers advantages for solution formulations as the salts may dissolve more quickly and / or more predictably than other forms of the active agent. We have found that salmeterol hyaluronate according to the invention has desiccant properties such that in a humid environment the particulate material may swell slightly whilst avoiding agglomeration. When blended with a carrier such as lactose the salmeterol hyaluronate salt of the invention appear to inhibit undesired carrier agglomeration and may inhibit adhesion of drug substance to carrier. Hence when blended with a carrier such as lactose the salts of the invention may experience reduced loss of fine particle mass (FPM) on storage especially under humid conditions.

According to a further aspect of the invention, there is provided a process for preparing a salt of the invention which comprises mixing a solution of the active agent with the free acid of the biodegradable polymeric sugar and recovering the resulting salt.

Another process for preparing a salt of the invention comprises spray drying a solution (e.g. an aqueous solution) of the active agent and the biodegradable polymeric sugar in the form of its free acid.

The free acid of the polymeric sugar may be obtained by reaction of a salt, e.g. a sodium salt, of the sugar with a strong acid, e.g. HCl, prior to reaction with the active agent. A reduction in molecular weight is expected during this process.

FIGURES

Figure 1 shows the 13C CP-MAS solid-state NMR spectra of salmeterol (bottom), hyaluronic acid (top) and salmeterol hyaluronate (middle) prepared according to Example 1.

Figure 2 shows the IR spectra of salmeterol (top), hyaluronic acid (bottom) and salmeterol hyaluronate (middle) prepared according to Example 1.

Figure 3 shows XRPD profiles for hyaluronic acid (middle), sodium hyaluronate (bottom) and salmeterol hyaluronate (top) (prepared according to Example 1).

Figure 4 shows the IR spectra of 4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (top), hyaluronic acid (bottom) and 4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol hyaluronate (middle) prepared according to Example 3.

Figure 5 shows the IR spectra of salbutamol (top), hyaluronic acid (bottom) and salbutamol hyaluronate (middle) prepared according to Example 4.

Figure 6 shows the IR spectra of *N*-{2-[4-((*R*)-2-Hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)

ethylamine (Compound A) free base(top) hyaluronic acid (middle) and Compound A Hyaluronate (bottom)

Figure 8 is a bar graph showing the effect on fine particle mass of Compound A hydrochloride (control) and Compound A Hyaluronate following storage at 30°C/65%RH. The measurements represent the mean fine particle mass of the compound deposited in Stage 2 of a reduced Anderson cascade impactor, expressed as μg (white bars) or % emitted dose (grey bars) and % nominal dose (black bars). The columns represent the following measurements (from left to right): Control at initial timepoint; control after 1 week at 30°C/65%RH, control after 2 weeks at 30°C/65%RH, HA salt at initial timepoint; HA salt after 1 week at 30°C/65%RH, HA salt after 2 weeks at 30°C/65%RH.

Figure 7 shows the IR spectra of Compound B free base(top) hyaluronic acid (middle) and Compound B Hyaluronate (bottom)

For a better understanding of the invention, the following Examples are given by way of illustration.

EXAMPLES

Analytical methods

XRPD analysis shown in Figure 1 was performed on a Bruker X-ray powder diffractometer, Model D8 Advance, serial number ROE 2357. The method runs from 2 to 40 degrees 2-Theta with a 0.0145 degree 2-Theta step size and a 1 second collection time at each step.

The X-ray powder diffraction (XRPD) analysis of Example 3 (shown in Figure 2) was performed on a PANalytical X'Pert Pro powder diffractometer, model PW3040/60, serial number DY1850 using an X'Celerator detector. T

The infrared absorption spectra were recorded at 2 cm-1 resolution over the wavenumber range 4000 to 650 cm-1 using a PerkinElmer Spectrum One FT-IR spectrometer equipped with a PerkinElmer Universal ATR (attenuated total reflection) sampling accessory. The ATR crystal used was a diamond / zinc selenide composite.

1H NMR spectra were acquired on a 400MHz Bruker DPX400 spectrometer at 300K. Sample was dissolved in CDCl3 or dmso-d6 and chemical shifts were reported in ppm relative to the TMS signal at 0 ppm.

Throughout the examples, the following abbreviations are used:
IMS: Industrial methylated spirits

Intermediate 1

Preparation of hyaluronic acid from sodium hyaluronate

A mixture of sodium hyaluronate (Bioiberica, MW ~500,000 Da, 40g) and acetone (250ml) was stirred mechanically at 20-23°C. A mixture of acetone (70ml) and water (100ml) was added and the slurry stirred at 20-23°C for *ca* 10min. A solution of 2M hydrochloric acid (150ml) and acetone (100ml) was then added over 12min at a batch temperature of 20-23°C. The resultant slurry was stirred at 20-23°C for 2h 20min.

The slurry was filtered under nitrogen and washed with a mixture of acetone and water (3:1, 4 x 400ml). The last wash was allowed to percolate through and the pH of the final wash was neutral. Finally the wet cake was washed with IMS (2 x 80ml). The solid was pulled dry under nitrogen and dried *in vacuo* at 20-25°C for 18h to give the product (37.64g) as a white free flowing solid.
Sodium content 0.2%w/w.
Measured viscosity (cP) 4.06 (in water) giving a predicted molecular weight of ~60,000 Da.

Intermediate 2

Preparation of hyaluronic acid in IMS/water from sodium hyaluronate

Sodium hyaluronate (30g) was suspended in IMS (400ml). Then 2M hydrochloric acid (75ml) was added in one charge followed by more IMS (60ml). The suspension was stirred for 1h. The slurry was filtered on a sintered glass funnel and washed with IMS: water (3:1, 2 x 400ml), IMS: water (2.5:1, 2 x 400ml) and finally with IMS (2 x 200ml). The product was dried *in vacuo* at 40°C to give 26.5g of the product as a free flowing powder.
Sodium content 0.4%w/w sodium
Measured viscosity (cP) 2.80 (in water) giving a predicted molecular weight of ~40,000 Da.

NMR spectrum shown in Figure 1 (top trace).
IR spectrum shown in Figure 2 (bottom trace).

Example 1

Synthesis of salmeterol hyaluronate

A suspension of salmeterol free base (317.5g) in IMS (3175 ml) was stirred mechanically and heated to ca 30-35°C to give a clear solution. To this was added hyaluronic acid (Intermediate 2, 125.1g). The suspension was stirred for 18h at *ca* 30°C then filtered and washed with IMS. Each time *ca* 300-500ml of wash was applied and allowed to percolate through under gravity. The washes were monitored by HPLC for residual salmeterol. Once the wash showed absence of salmeterol by HPLC, the solid was then pulled dry and dried further at *ca* 35-40°C to give 189.9g of polymeric salt with a loading of 34.1%w/w (weight of salmeterol/weight of salt). The loading and identity of the released drug was confirmed by HPLC analysis.

Release of drug from the hyaluronate salt

The drug was released by dissolving a known weight (10 -100mg) of salt in pH6 buffer (10-100ml). The released drug was assayed against a standard solution of the drug by HPLC analysis. To prepare a drug reference sample, 10mg of the free drug was dissolved in acetonitrile/water (10ml) in a volumetric flask and a known volume of this was made up to 1ml with acetonitrile/water and injected on HPLC (for HPLC conditions see table below). In a similar way, a known quantity of the salt was dissolved in pH6 buffer and a known volume of this solution was injected on HPLC. The loading was determined by comparative HPLC assay. Release of drug from the salt was typically quantitative.

HPLC conditions for assay and identification of eluted drug by comparative retention time:

The following conditions were used for HPLC analysis.

Parameter	Value
Analytical Column	Luna C18(2), 3µm
Mobile Phase	Water/acetonitrile gradient
Detection	UV, wavelength analyte dependant (Note: Wavelength NLT 220nm recommended)
Injection Volume	1µl

Figure 1 shows the 13C CP-MAS solid-state NMR spectra of salmeterol (bottom), hyaluronic acid (top) and the polymeric salt (middle). The resonances of salmeterol are still visible in the polymeric salt but are very broad suggesting that the salmeterol molecule is less mobile than in the pure solid form. This is consistent with the salmeterol molecule being part of a polymeric species.

Figure 2 shows the IR spectra of salmeterol (top), hyaluronic acid (bottom) and the polymeric salt (middle). Key features of the spectrum of the polymeric salt indicate that the interaction of salmeterol and hyaluronic acid is via the formation of an amine/carboxylic acid salt, i.e. lack of neutral amine stretch, presence of ionised carboxylate and absence of carboxylic acid functionality.

Figure 3 shows XRPD profiles for hyaluronic acid (middle), sodium hyaluronate (bottom) and salmeterol hyaluronate (top). All these traces are characteristic of amorphous substance.

Example 2

Comparative performance of dry powder compositions containing salmeterol hyaluronate and salmeterol xinafoate

Salmeterol hyaluronate prepared as described in Example 1 was micronised using a 4" APTM microniser.

Blends A and B as tabulated below (Table 1), were prepared by the following procedure: The blends were formulated by placing approximately half of the weighed lactose into a Waring blender. All of the drug substance (salmeterol xinafoate or salmeterol hyaluronate) was then added, followed by the remaining lactose. The blender was operated for 5min at the low speed setting.

Table 1.

Blend	Contents of Blend	Amount (per dose)	Amount (g)	Amount (%)
A	Micronised Salmeterol Hyaluronate *	36.76µg to 12.5mg	0.294	0.294
	Lactose monohydrate **		99.706	99.706
	8.7% fines			
B	Salmeterol Xinafoate ***	18.16µg to 12.5mg	0.145	0.145
	Lactose monohydrate **		99.855	99.855

	8.7% fines			

' 34%w/w salmeterol loading, particle size 5μm, measured using Malvern Dispersion Particle size analysis in isooctane / lecithin.

'* Measured by Malvern Dispersion Particle size analysis in isooctane / lecithin. Fines epresents % v/v of particles less than 15μm.

'** Approx. 2μm. Salt to base conversion 0.6883.

Unsealed jars containing blends A and B were placed on stability for 4 weeks storage at 40°C/75% relative humidity.

X-ray powder diffraction confirmed that the material remained amorphous after storage. The particle size was measured by laser diffraction using an isooctane/lecithin dispersant. The volume mean diameter increased from 5.9 μm initially to 7.8 μm after storage. This small increase is believed to be attributable to swelling as a result of moisture uptake. Thermogravimetric analysis confirmed that the particles had picked up moisture and gravimetric vapour sorption showed that the moisture capacity was around 20% initially. Scanning electron microscopy before and after storage showed no discernable differences.

A modified twin stage impinger analysis, British Pharmacopoeia (Method A) was performed at 60L/min using a vibrating hopper to feed the blend (130 mg) into a turbulent air flow. The blends were tested pre and post storage and the salmeterol base content was quantified by High Performance Liquid chromatography. The results are tabulated below (Table 2).

Table 2.

Blend	Pre-Storage (μg/dose)	Post-Storage at 40/75 (μg/dose)
	Stage 2 / Sum of Stage 1 and 2	Stage 2 / Sum of Stage 1 and 2
A	18.1 / 118.4	12.1 / 99

B	18.6 / 109.5	None detected / 4.4

Blend	Pre Storage Mean Stage 2 (%)	Post-Storage at 40/75 Mean Stage 2 (%)
A	15.3	12.2
B	16.9	None detected

To ensure rigorous testing of the salts of the invention harsh storage conditions (high temperature and relative humidity) which are generally expected to be deleterious to pharmaceutical formulations were used.

The fine particle fraction measured as percentage Stage 2 deposition of the salmeterol hyaluronate/lactose blends is of the same order as that of the salmeterol xinafoate/lactose blends, but shows far greater stability on storage, with no apparent agglomeration after 1 month at 40°C/75% relative humidity. However, after storage at 40°C/75% relative humidity the salmeterol xinafoate/lactose blend was highly agglomerated and could not be tested.

It can be concluded that even at very low dosing levels (in this case 0.294% w/w) and even under these very aggressive testing conditions the micronised polymeric hyaluronate salt appear to have a significant inhibitory effect on carrier agglomeration. The loss of fine particle mass (FPM) was remarkably low.

Example 3

Synthesis of 4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol hyaluronate

A suspension of 4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1g) in IMS (10 ml) was stirred mechanically to give a clear solution. To this was added hyaluronic acid (0.5g). The suspension was stirred for 18h at *ca* 30°C then filtered and washed with IMS. Each time *ca* 10ml of wash was applied and allowed to percolate through under gravity. The washes were monitored by HPLC for residual drug. Once the wash showed absence of drug substance by HPLC,

the solid was then pulled dry and dried *in vacuo* at 25°C to give 0.71g of resinate with a loading of 29.6%w/w. The loading and identity of the released drug was confirmed by HPLC analysis using the general method described in Example 1. Release of drug from the salt was typically quantitative.

IR spectra of the salt (middle) and comparison with hyaluronic acid (bottom) and original drug substance (top) are shown in Figure 4. Key features of the spectrum of the polymeric salt indicate that the interaction of drug and hyaluronic acid is via the formation of a carboxylic acid salt, i.e. presence of ionised carboxylate and the reduction of carboxylic acid functionality when compared to the spectrum of hyaluronic acid. This would imply that protonation of the secondary amine functionality of the drug has occurred.

Example 4

Synthesis of salbutamol hyaluronate

Salbutamol base (0.5g) was suspended in IMS (22ml), stirred at *ca* 20-22°C to give an almost clear solution. Hyaluronic acid (1g) was added and the suspension was stirred at 20-22°C for 18h.

The suspension was filtered, washed with IMS (4 x 50ml) and then with IMS (90ml), pre-warmed to ca 30°C. The solid was dried *in vacuo* at 20-25°C to constant weight to give the product as a white free flowing powder (1.23g, 18.6%w/w loading). The loading and identity of the released drug was confirmed by HPLC analysis using the general method described in Example 1. Release of drug from the salt was typically quantitative.

IR spectra of the salt (middle) and comparison with hyaluronic acid (bottom) and original drug substance (top) are shown in Figure 5. Key features of the spectrum of the polymeric salt indicate that the interaction of salbutamol and hyaluronic acid is via the formation of a carboxylic acid salt, i.e. presence of ionised carboxylate and the reduction of carboxylic acid functionality when compared to the spectrum of hyaluronic acid. This would imply that protonation of the secondary amine functionality of salbutamol has occurred.

Example 5

Preparation of *N*-{2-[4-((*R*)-2-Hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine Hyaluronate :

A suspension of *N*-{2-[4-((*R*)-2-Hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine (Compound A) (3.16g) in industrial methylated spirit (IMS) 10ml) was stirred mechanically to give a solution. To this was added Hyaluronic acid (15g). The suspension was stirred for 18h at 40°C then filtered and washed with IMS. Each time ca 30ml of wash was applied and allowed to percolate through under gravity. The washes were monitored by HPLC for residual drug. Once the wash showed absence of drug substance by HPLC, the solid was then pulled dry and dried further at *ca* 35°C to give 17.4g of drug resinate with a loading of 16%w/w.

The IR spectra of Compound A free base(top) hyaluronic acid (middle) and Compound A Hyaluronate (bottom) are given in Fig 6.

Release of the drug from resinate and measurement of drug loading were carried out as for Example 1.

The resinate was spray dried from an aqueous THF solution to provide spray dried drug resinate with particle size of 2 to 5 microns suitable for inhaled application using a Niro Mobile Minor spray drier. The drug loading remained unchanged after spray drying.

Comparative performance of dry powder compositions containing Compound A hyaluronate and Compound A monohydrochloride salt

The use of hyaluronic acid in dry powder inhalation formulations was investigated.

Each formulation was manufactured as 0.08%w/w (10µg/12.5mg lactose) blends. The control formulation comprised micronised Compound A monohydrochloride salt with identical lactose to the hyaluronate formulation (Blend 2) .

Blends 1 and 2 as tabulated below (Table 3), were prepared by the following procedure: The blends were manufactured by placing approximately half of the dispensed lactose into a 1L QMM bowl . The drug substance (Compound A monohydrochloride salt or Compound A hyaluronate) was then added and rinsed with lactose (x3) followed by addition of the remaining lactose. The QMM blender was operated for a total 10min at 600rpm. The blending process was stopped briefly after 5 minutes in order to scrape blend off the vessel walls.

Table 3

Blend	Contents of Blend	Amount (per dose)	Amount (g)	Amount (%)
1	Micronised Compound A monohydrochloride *	10µg to 12.5mg	0.460	0.092
	**Lactose monohydrate		499.54	99.908
	10% fines			
2	Compound A_Hyaluronate***	10µg to 12.5mg	4.040	0.808
	**Lactose monohydrate		495.960	99.192
	10% fines			

1. *Approx 4µm, salt to base conversion (1.119)

52. ** Measured by Malvern Dispersion Particle size analysis in isooctane / lecithin. Fines represents % v/v of particles less than 15µm.

3. ***10%w/w Compound A monohydrochloride loading, particle size 2µm, measured using Malvern Dispersion Particle size analysis in isooctane / lecithin.

Each formulation was analysed by high performance chromatography (HPLC) for content uniformity in order to verify blend homogeneity and also in order to confirm drug concentration for each formulation.

Each blend was stored on stability for 1 or 2wks at 30°C/65%RH in order to probe the effects of storage physical stability, blend exposure at 40/75%RH for 2 weeks was undertaken in order to investigate chemical stability effects. All physical/chemical stability in vitro performance tests were performed using a model dry powder device attached to a reduced Anderson cascade impactor. The data was reported as % emitted dose in order to mitigate the effects of fill weight differences in model dry powder device. The data for the formulations indicated that the emitted dose for both formulations was declining over time. Figure 8 shows the effect on fine particle mass following storage at 30°C/65%RH, expressed as µg or % emitted/nominal.

Example 6

Preparation of 2-[(*S*)-1-(8-methylaminooctyl)-pyrrolidin-3-yl]-2,2-diphenylacetamide Hyaluronate :

Hyaluronic acid (48.5g,) was added to a solution of 2-[(*S*)-1-(8-methylaminooctyl)-pyrrolidin-3-yl]-2,2-diphenylacetamide (Compound B) (5g) in IMS (300ml) and washed in with IMS (100ml). The white suspension was stirred at 20-25°C for 18h. The product was collected by filtration under nitrogen and then washed with IMS (2 x 150ml) under vacuum, then with IMS (2 x 150ml) which was allowed to percolate under gravity and finally with more IMS (2 x 50ml). The washings were monitored for drug content and considered complete once the level of drug in the washes was less than 5mg in a 50ml wash. The washed solid was then dried *in vacuo* at 30°C for 3h and then 20-25°C for 18h and then equilibrated at room temperature for ca 2h to give 46.71g (14.4%w/w loading as by weight gain) of the resinate as a free flowing white powdery solid.

The IR spectra of Compound B free base(top) hyaluronic acid (middle) and Compound B Hyaluronate (bottom) are given in Fig 7.

Release of the drug from resinate and measurement of drug loading were carried out as for Example 1.

The resinate was spray dried from an aqueous THF solution to provide spray dried drug resinate with particle size of 2 to 5 microns suitable for inhaled application using a Niro Mobile Minor spray drier. The drug loading remained unchanged after spray drying.

Product performance of dry powder compositions containing 2-[(*S*)-1-(8-methylaminooctyl)-pyrrolidin-3-yl]-2,2-diphenylacetamide hyaluronate

Blend was prepared by the following procedure:

An excipient preblend was generated by combining the cellobiose and approximately half the lactose into a blending jar and mixing for 5 minutes using a Turbula T2 mixer at 96 rpm. The remaining lactose was transferred to the blending jar and mixed for 2 x 5 minutes at 96 rpm in the Turbula mixer.

A drug preblend was prepared by removing approximately half the excipient preblend and adding required drug contents to mixing jar. The jar contents were mixed for 5 minutes at 96rpm. The remaining portion of the excipient preblend was transferred to the mixing jar and mixed for 3 x 5 minutes at 96 rpm in the Turbula mixer. Transfer the blend to an antistatic bag and allow it to equilibrate for 8 hours prior to filling into blister strips.

Table 4

Blend	Contents of Blend	Amount (per dose)	Amount (g)	Amount (%)
A	Spray Dried Compound B Hyaluronate Salt Cellobiose Octaacetate Lactose monohydrate (8.7% fines)	 115*µg to 12.5mg	 10.7 2.5 102.5	 0.92*

* Compound B Base

Approximately half the blend prepared above was filled into blister strips immediately after preparation using a perforated bed dry powder filler. The remaining half was filled 24 hours later after exposure to ambient conditions in the fill area.

A next generation impactor (NGI-Next Generation Impactor Consortium), USP, was performed at 60L/min with a DPI device fitted to unit throat. The blends were tested pre and post storage and Compound B base content was quantified by High Performance Liquid chromatography. The results are tabulated below (Table 5).

Table 5

Blend	Initial Testing Mean %FPM (n=3)	Initial Testing Mean ED%*, calc (n=3)	Post Storage - 24 hrs,Ambient Mean %FPM (n=3)	Post Storage- 24 hrs,Ambient Mean ED%*, calc (n=3)
A	22.3	26.9	19.8	23.9

*ED – emitted dose, calculated as total material in impactor

All references including patent and patent applications referred to in this application are incorporated herein by reference to the fullest extent possible.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A pharmaceutical formulation adapted for administration by inhalation, comprising a salt of a biodegradable polymeric sugar comprising acidic groups and a pharmaceutically active agent comprising one or more basic groups, and a pharmaceutically acceptable carrier or diluent.

2. A pharmaceutical formulation according to claim 1 wherein the biodegradable polymeric sugar is selected from hyaluronic acid, chondroitin sulfate, alginic acid, heparan sulfate, heparin, dermatan sulfate and keratan sulfate.

3. A pharmaceutical formulation according to claim 1 or 2 wherein the biodegradable polymeric sugar is hyaluronic acid.

4. A pharmaceutical formulation according to any one of the preceding claims wherein the pharmaceutically active agent contains one or more amine groups.

5. A pharmaceutical formulation according to any one of the preceding claims wherein the pharmaceutically active agent has a pKa $\geq$6 and the biodegradable polymeric sugar comprises carboxylic acid groups.

6. A pharmaceutical formulation according to claim 5 wherein the pharmaceutically active agent has a pKa of 7-12.

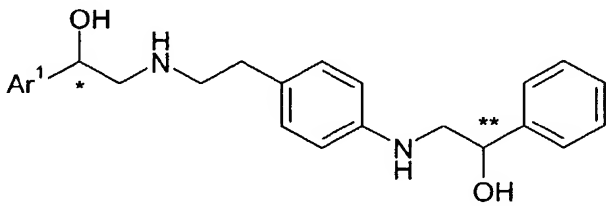
7. A pharmaceutical formulation according to any one of claims 1, 2 or 4 wherein the pharmaceutically active agent has a pKa $\geq$4 and the biodegradable polymeric sugar comprises sulfonic acid groups.

8. A pharmaceutical formulation according to claim 7 wherein the pharmaceutically active agent has a pKa of 4-12.

9. A pharmaceutical formulation according to any one of the preceding claims wherein the pharmaceutically active agent is selected from β_2-adrenoreceptor agonists, anti-inflammatory agents, anticholinergic agents, antiinfective agents and antihistamines.

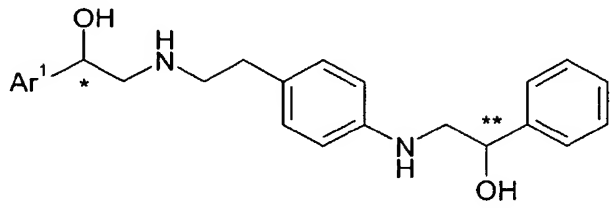
10. A pharmaceutical formulation according to claim 9 wherein the pharmaceutically active agent is a β_2-adrenoreceptor agonist.

11. A pharmaceutical formulation according to claim 10 wherein the β_2-adrenoreceptor agonist is selected from salmeterol, (R)-salmeterol, salbutamol, (R)-salbutamol, formoterol, (R,R)-formoterol, fenoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerobuterol, reproterol, bambuterol, terbutaline,
3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl) benzenesulfonamide,
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide,
4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol,
4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol,
QAB-149, LAS-32521,
[R-(R*,R*)]-8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolone (CAS-137888-11-0);
N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;
5-[(R)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one;
and compounds of the formula:



wherein Ar^1 is 4-amino-3,5-dichlorophenyl or 3-formylamino-4-hydroxyphenyl, and the stereochemistry at *C and **C is (RS) and (RS), (R) and (R), (S) and (S), (R) and (S), or (S) and (R).

12. A pharmaceutical formulation according to claim 11 wherein the compound of formula



is *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine.

13. A pharmaceutical formulation according to claim 11 wherein the β_2-adrenoreceptor agonist is salmeterol.

14. A pharmaceutical formulation according to any one of the preceding claims wherein the salt is in particulate form.

15. A pharmaceutical formulation according to claim 14 wherein the salt has a MMAD of 1-10μm.

16. A pharmaceutical formulation according to claim 14 or 15 which is a dry powder formulation.

17. A pharmaceutical formulation according to claim 16 wherein the pharmaceutically acceptable carrier is lactose.

18. A method for the prophylaxis or treatment of disease in a mammal which comprises administration by inhalation of a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 17.

19. A method according to claim 18 wherein the disease is a respiratory disease.

20. A salt of a biodegradable polymeric sugar comprising acidic groups and a pharmaceutically active agent containing one or more amine groups.

21. A salt according to claim 20 wherein the biodegradable polymeric sugar is selected from hyaluronic acid, chondroitin sulfate, alginic acid, heparan sulfate, heparin, dermatan sulfate and keratan sulfate

22. A salt according to claim 21 wherein the biodegradable polymeric sugar is hyaluronic acid.

23. A salt according to any one of claims 20 to 22 wherein the pharmaceutically active agent has a pKa ≥6 and the biodegradable polymeric sugar comprises carboxylic acid groups.

24. A salt according to claim 23 wherein the pharmaceutically active agent has a pKa of 7-12.

25. A salt according to claim 20 or claim 21 wherein the pharmaceutically active agent has a pKa ≥4 and the biodegradable polymeric sugar comprises sulfonic acid groups.

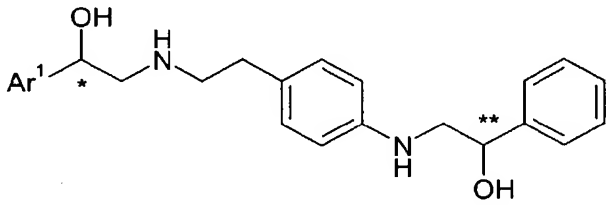
26. A salt according to claim 25 wherein the pharmaceutically active agent has a pKa of 4-12.

27. A salt according to any one of claims 20 to 26 wherein the pharmaceutically active agent is selected from β_2-adrenoreceptor agonists, anti-inflammatory agents, anticholinergic agents, antiinfective agents and antihistamines.

28. A salt according to claim 27 wherein the pharmaceutically active agent is a β_2-adrenoreceptor agonist.

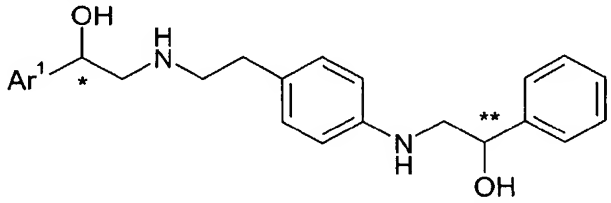
29. A salt according to claim 28 wherein the β_2-adrenoreceptor agonist is selected from salmeterol, (R)-salmeterol, salbutamol, (R)-salbutamol, formoterol, (R,R)-formoterol, fenoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerobuterol, reproterol, bambuterol, terbutaline,
3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl) benzenesulfonamide,
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide,

4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol,
4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol,
QAB-149, LAS-32521, [R-(R*,R*)]-8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolone (CAS-137888-11-0);
N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;
5-[(R)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one;
and compounds of the formula:



wherein Ar^1 is 4-amino-3,5-dichlorophenyl or 3-formylamino-4-hydroxyphenyl, and the stereochemistry at *C and **C is (RS) and (RS), (R) and (R), (S) and (S), (R) and (S), or (S) and (R).

30. A salt according to claim 29 wherein the compound of formula



is *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine.

31. A salt according to claim 29 wherein the β_2-adrenoreceptor agonist is salmeterol.

32. A salt according to any one of claims 20 to 31 for use in medical therapy.

33. The use of a salt according to any one of claims 20 to 31 in the manufacture of a medicament adapted for administration by inhalation.

34. The use of a salt according to any one of claims 20 to 31 in the manufacture of a medicament for administration by inhalation in the prophylaxis or treatment of a respiratory disease.

35. A process for preparing a salt according to any one of claims 20 to 31 which comprises mixing a solution of the active agent with the biodegradable polymeric sugar and recovering the resulting salt.

FIGURE1

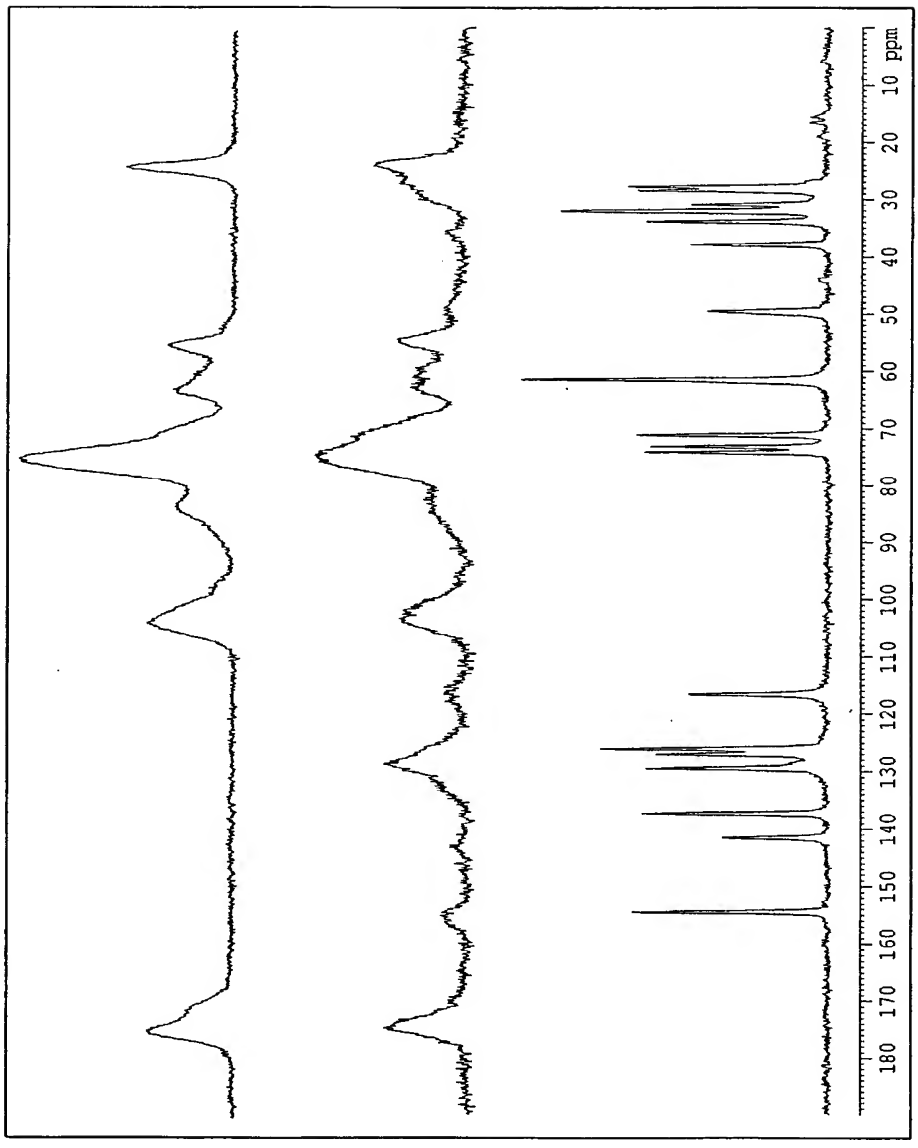


FIGURE 2

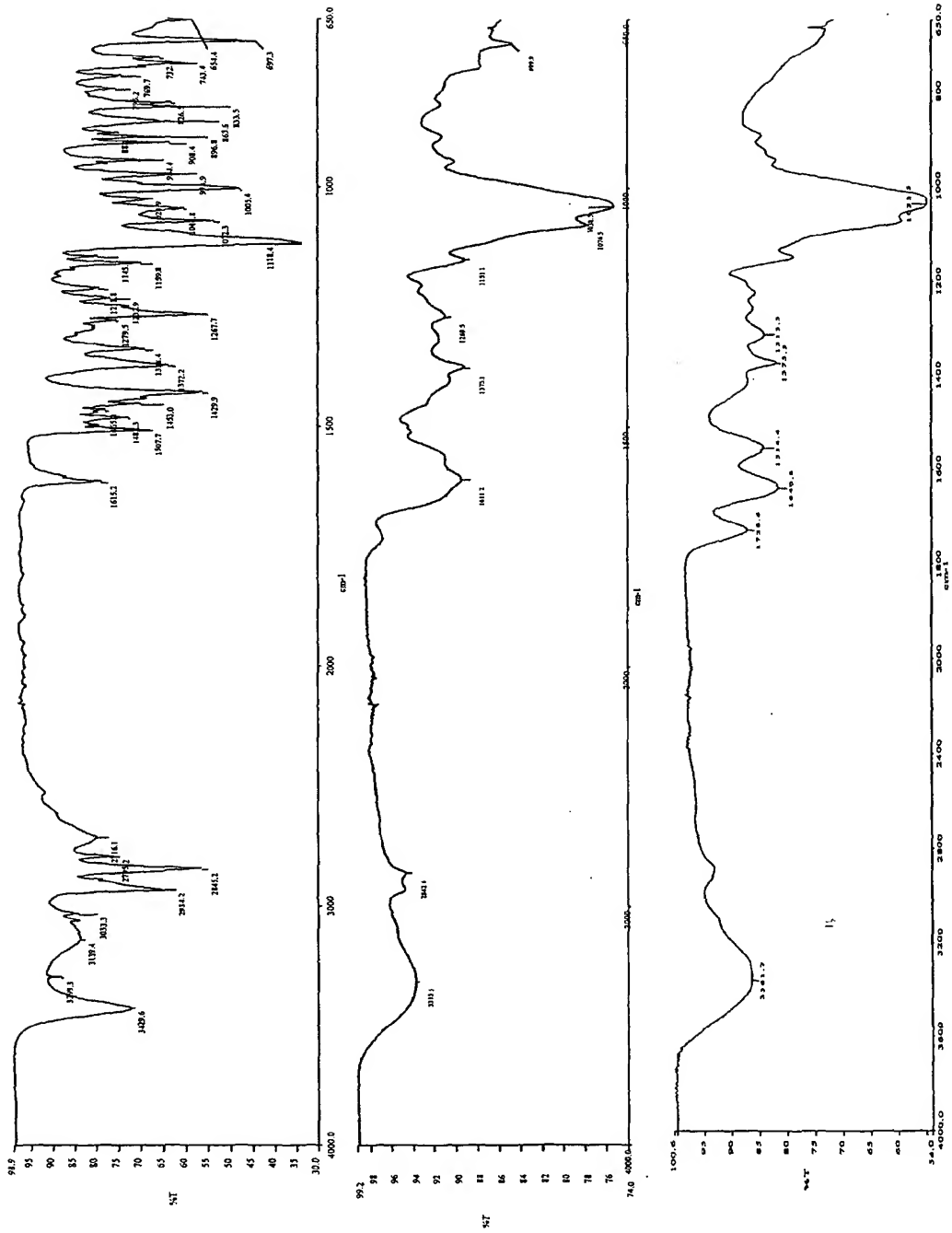


FIGURE 3

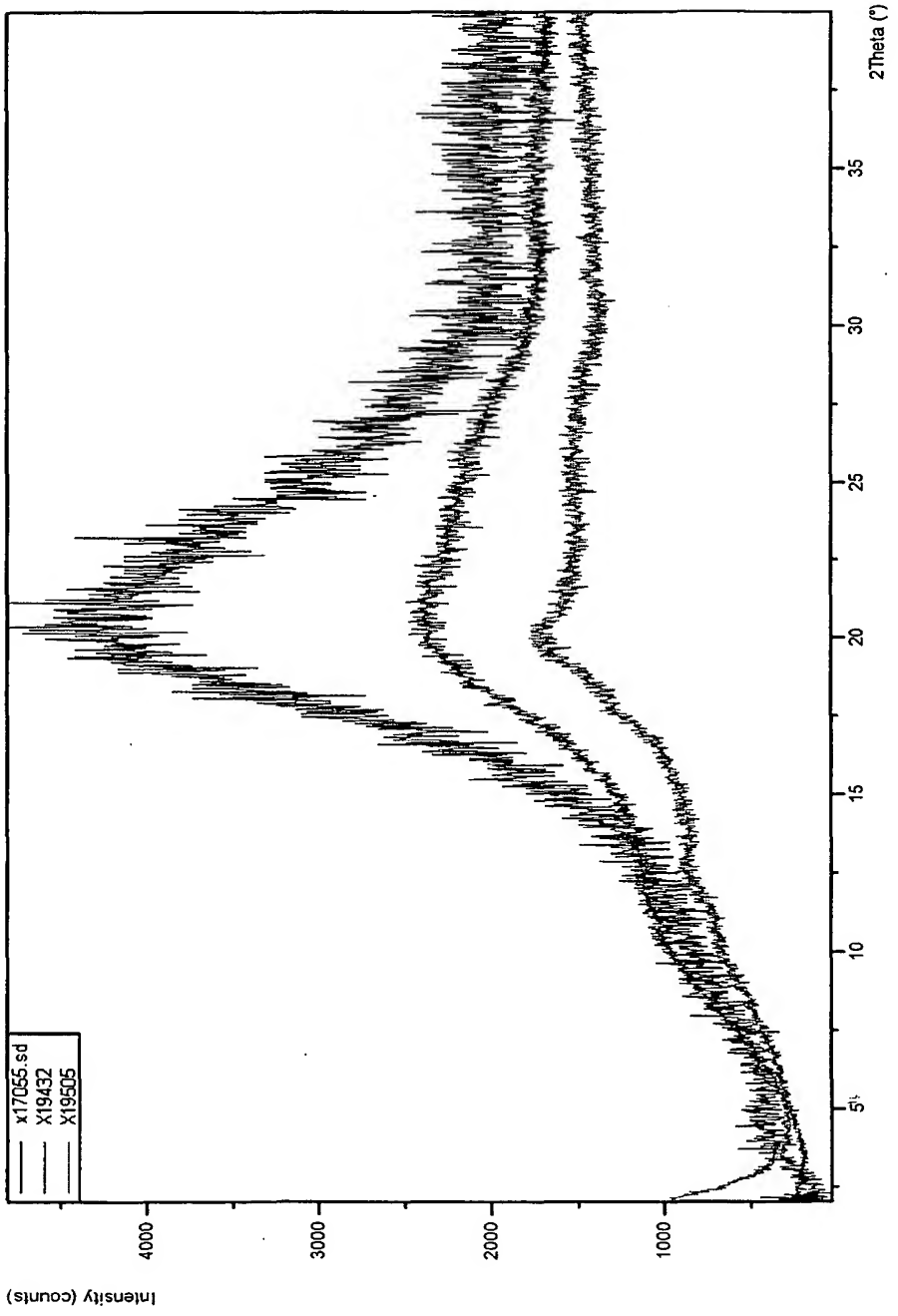

x17055.sd
X19432
X19505
Intensity (counts)
4000
3000
2000
1000
5
10
15
20
25
30
35
2Theta (°)

FIGURE 4:

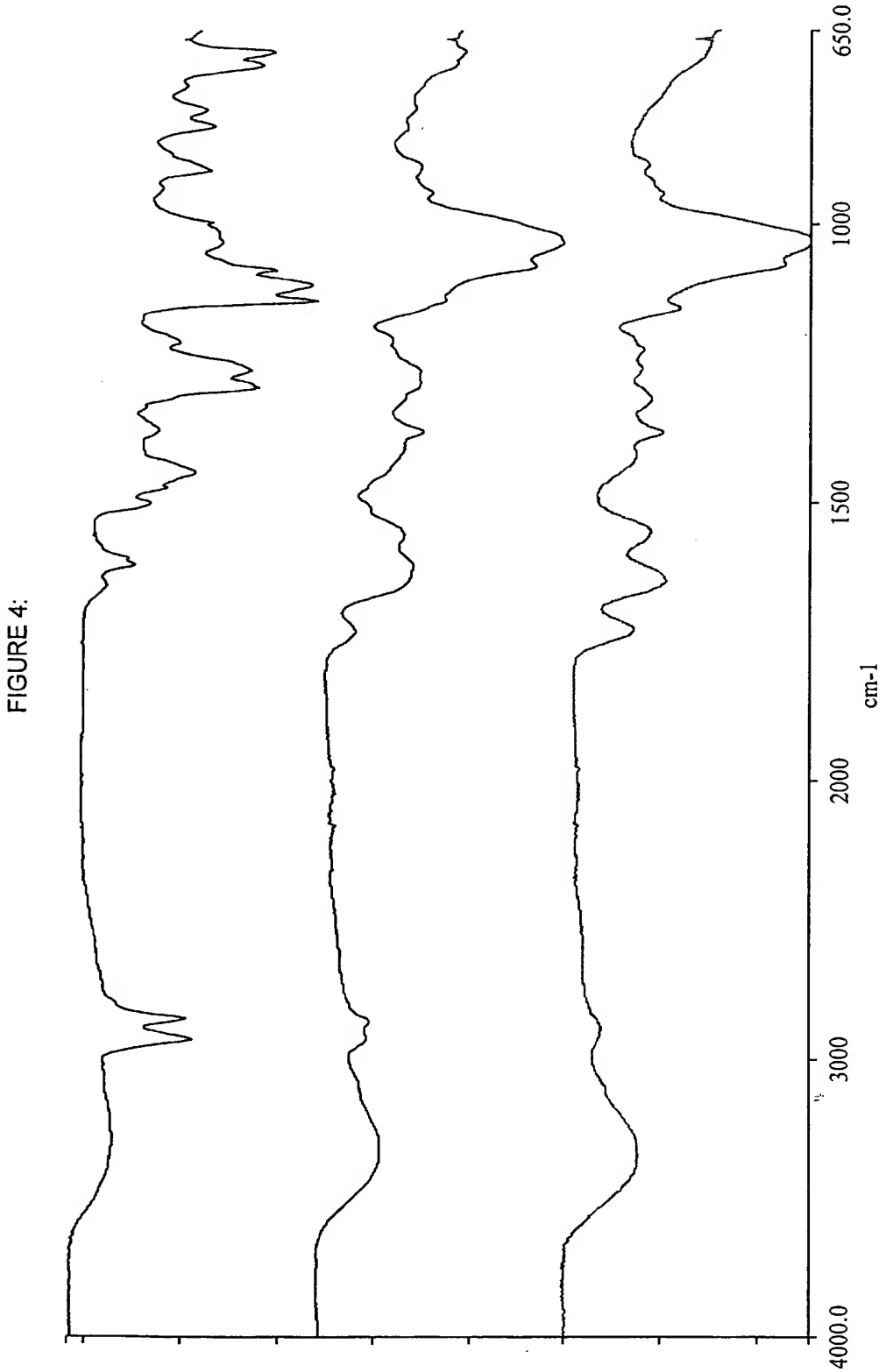


FIGURE 5:

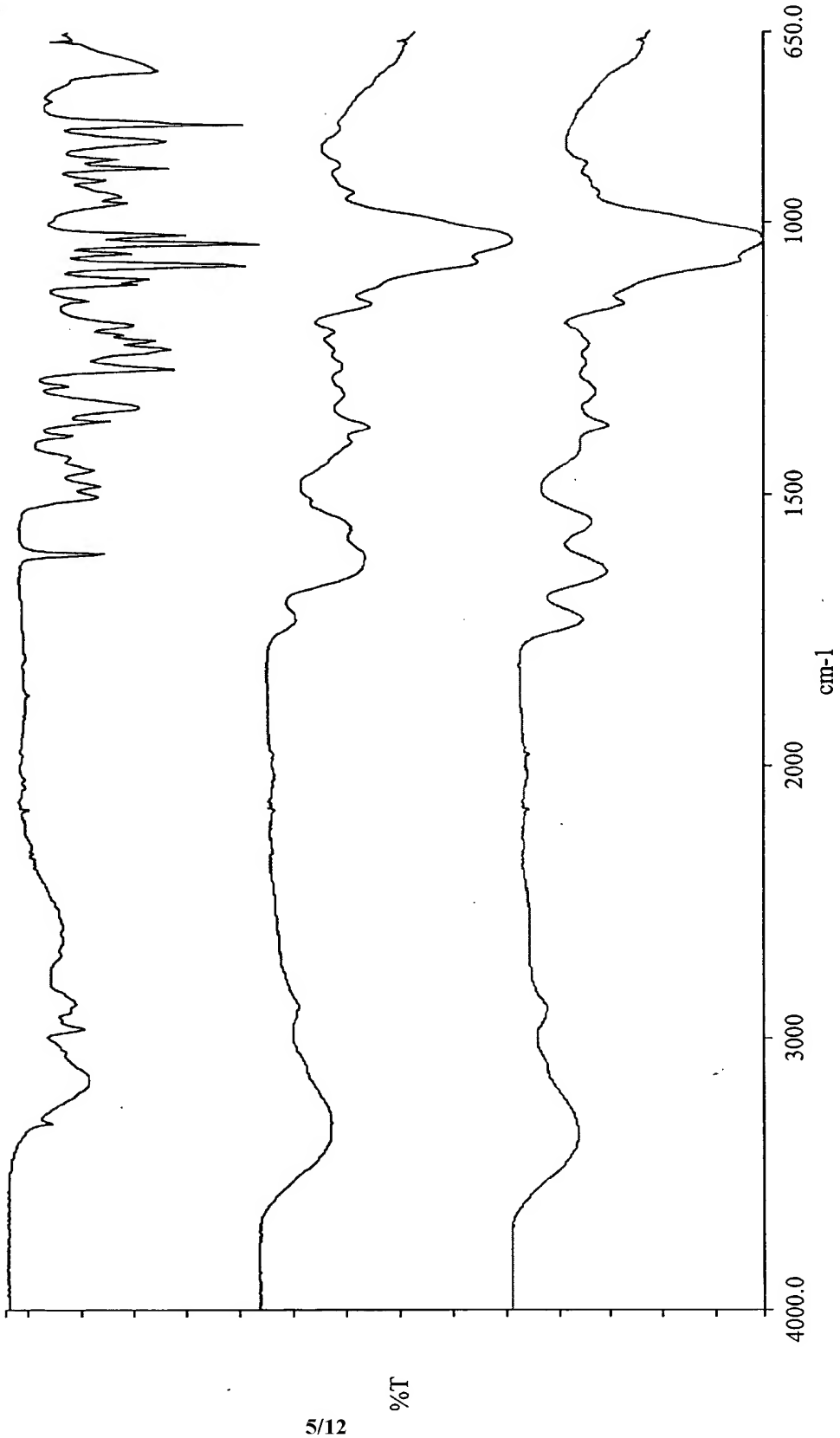


FIGURE 6

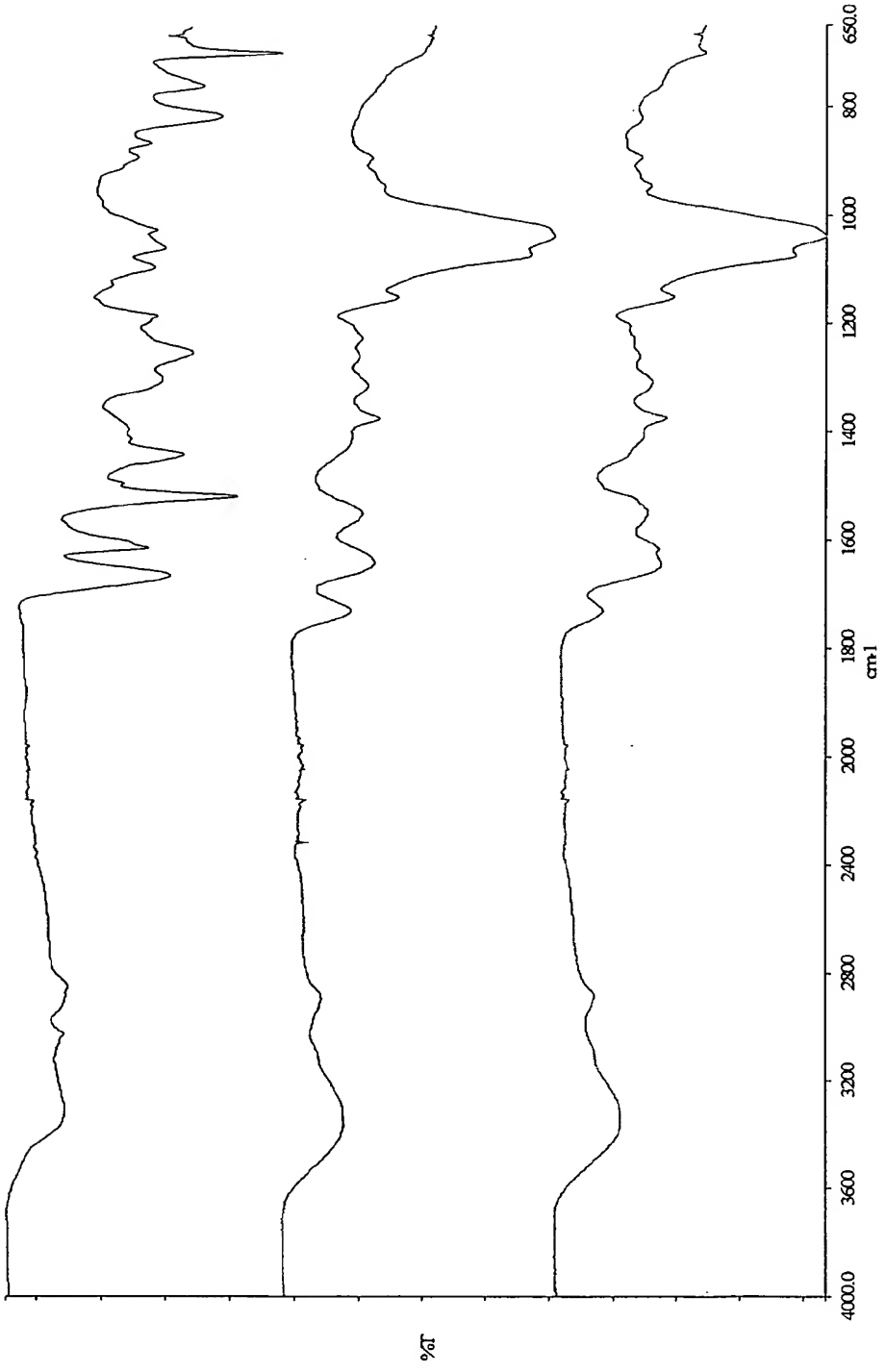

%T
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
650.0
cm-1

FIGURE 7:

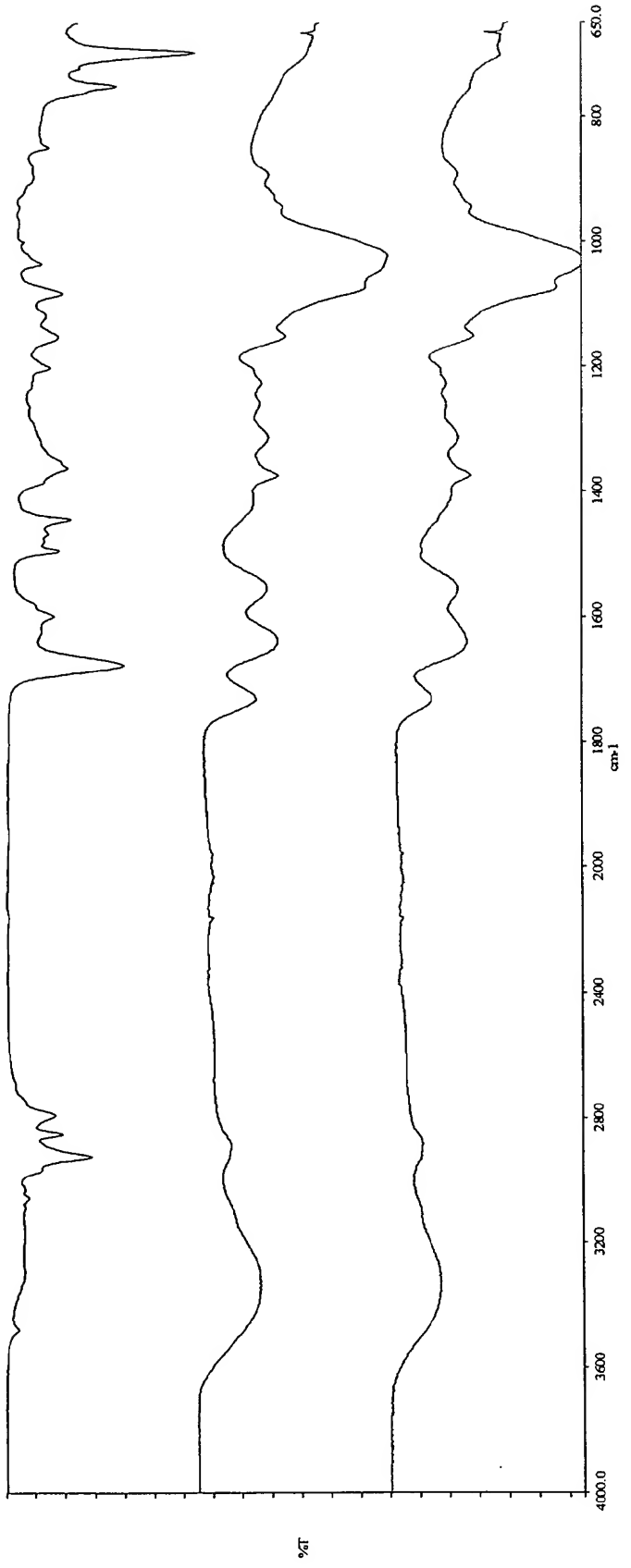

%T
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
650.0
cm-1

FIGURE 8